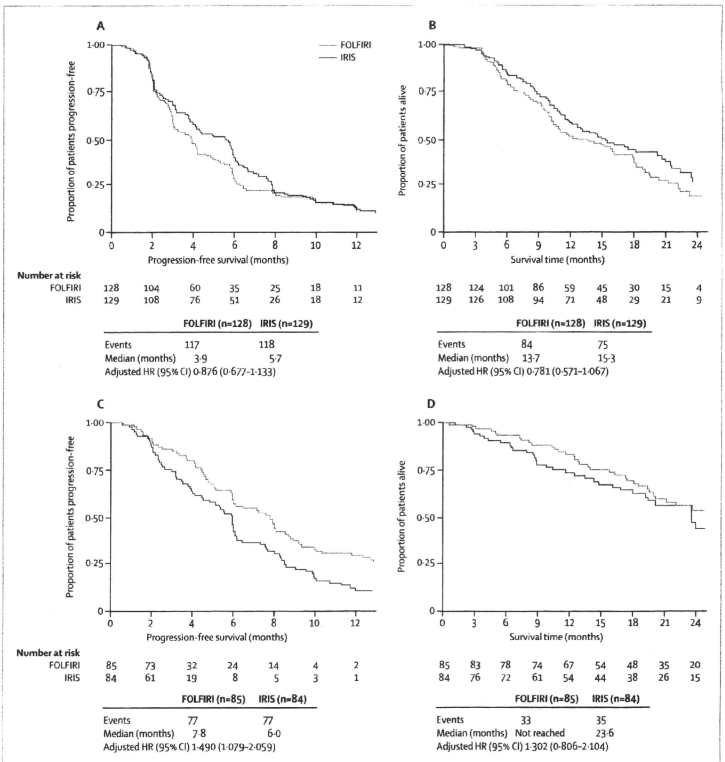

Figure 4: **Survival according to prior chemotherapy**
Progression-free survival with prior oxaliplatin (A). Overall survival with prior oxaliplatin (B). Progression-free survival without prior oxaliplatin (C). Overall survival without prior oxaliplatin (D). FOLFIRI=infusional fluorouracil, folinic acid, and irinotecan. IRIS=irinotecan plus 5-1. HR=hazard ratio.

When our trial was started, FOLFOX was already the standard first-line treatment worldwide, but because oxaliplatin had just been launched in Japan, patients who received prior chemotherapy regimens without oxaliplatin were also enrolled. In the subgroup that received prior oxaliplatin, the adjusted HR for progression-free survival of IRIS to FOLFIRI was 0·876 (95% CI 0·677–1·133) suggesting that IRIS was non-inferior to FOLFIRI after failure on oxaliplatin-containing regimens. In this subgroup, the median progression-free survival associated with IRIS was 5·7 months, and much better than the previously reported progression-free survival associated with FOLFIRI in patients who received prior chemotherapy with a fluoropyrimidine and oxaliplatin.[3,23] FOLFOX or FOLFIRI as the first-line chemotherapy and subsequent crossover in the second line is the most common treatment strategy for metastatic colorectal cancer, although there is no evidence of superiority of FOLFIRI over irinotecan alone. In Japan, the approved dose of irinotecan (150 mg/m^2, every 2 weeks) alone is lower than that in western countries, and monotherapy with irinotecan (350 mg/m^2, every 3 weeks) could not be used. Both IRIS

	FOLFIRI (n=211)			IRIS (n=210)			p value (grade 3–4)
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	
Neutropenia	179 (84·8%)	76 (36·0%)	34 (16·1%)	139 (66·2%)	54 (25·7%)	22 (10·5%)	0·0012
Leucopenia	170 (80·6%)	32 (15·2%)	1 (0·5%)	154 (73·3%)	32 (15·2%)	6 (2·9%)	0·5178
Anaemia	115 (54·5%)	13 (6·2%)	1 (0·5%)	156 (74·3%)	19 (9·0%)	2 (1·0%)	0·2221
Thrombocytopenia	63 (29·9%)	1 (0·5%)	1 (0·5%)	74 (35·2%)	0 (0·0%)	0 (0·0%)	0·4988
Diarrhoea	125 (59·2%)	10 (4·7%)	0 (0·0%)	167 (79·5%)	43 (20·5%)	0 (0·0%)	<0·0001
Fatigue	144 (68·2%)	7 (3·3%)	0 (0·0%)	153 (72·9%)	18 (8·6%)	0 (0·0%)	0·0242
Febrile neutropenia	3 (1·4%)	2 (0·9%)	0 (0·0%)	10 (4·8%)	10 (4·8%)	0 (0·0%)	0·0205
Mucositis or stomatitis	92 (43·6%)	1 (0·5%)	0 (0·0%)	102 (48·6%)	6 (2·9%)	0 (0·0%)	0·0677
Anorexia	129 (61·1%)	11 (5·2%)	0 (0·0%)	141 (67·1%)	23 (11·0%)	0 (0·0%)	0·0329
Nausea	111 (52·6%)	9 (4·3%)	0 (0·0%)	99 (47·1%)	4 (1·9%)	0 (0·0%)	0·2593

Data are number (%).

***Table 2:* Safety analysis**

and FOLFIRI showed longer median progression-free survival than reported in trials of monotherapy with irinotecan.[1,22] Thus, irinotecan-based regimens, such as FOLFIRI and IRIS, delivered every 2 weeks, should be considered after FOLFOX failure, especially in Japan. By contrast, in the subgroup of patients previously treated without oxaliplatin, progression-free survival was longer in the FOLFIRI group than in the IRIS group (HR 1·490, 95% CI 1·079–2·059). In this subset, prior fluorouracil monotherapy (oral, bolus) had failed in some patients. For these patients, FOLFIRI might have greater efficacy than IRIS. Nonetheless, even in this subgroup, median progression-free survival in the IRIS group was 6·0 months and no worse than that previously reported for second-line chemotherapy in patients refractory to fluorouracil alone.[3,24–26]

In each of the subgroups stratified by use or non-use of oxaliplatin, no differences were identified in other patient characteristics between the two groups. There is no clearly understood reason for the interaction between the presence or absence of oxaliplatin and therapeutic effects in the two groups. We speculate that a different mode of fluorouracil administration in FOLFIRI compared with prior therapy might work more effectively than S-1 for the patients without prior therapy with oxaliplatin, and that S-1 might have some salvage effects in patients who received FOLFOX involving bolus and infusional fluorouracil.

Our data have some limitations. First, progression-free survival, the primary endpoint, was assessed on the basis of disease progression established by the investigator at each medical institution. Therefore, caution should be used when our results are compared with those of other studies in which progression-free survival was centrally assessed. Second, around 40% of the patients in this trial were not previously treated with oxaliplatin, since FOLFOX therapy was approved in Japan only just before the study was started. Because FOLFOX is now widely used as first-line chemotherapy in Japan, patients should be carefully selected when our overall results are used to apply IRIS therapy in the clinical setting. However, we believe that the findings from subgroup analyses suggest that IRIS was better than FOLFIRI in patients who received an oxaliplatin-containing regimen as first-line chemotherapy.

In conclusion, progression-free survival with IRIS is not inferior to that with FOLFIRI in patients receiving second-line chemotherapy for metastatic colorectal cancer. IRIS therapy can be an additional treatment option for second-line chemotherapy in metastatic colorectal cancer.

Research in context

Systematic review

Before the study was initiated, we searched the PubMed database for relevant articles using search terms such as "metastatic colorectal cancer", "chemotherapy", "second line", and "phase 3". Based on the relevant articles obtained, the institutional review board reviewed the appropriateness as well as ethical and scientific aspects of the study, on which to base the approval of the study.

Interpretation

Our study demonstrates the non-inferiority of IRIS to FOLFIRI, one of international standard therapies for second-line chemotherapy of metastatic colorectal cancer; thus, IRIS is an option for second-line chemotherapy.

Contributors

IH, SM, NB, YS, HT, YK, MW, and KS, as a steering committee, participated in all phases of this study, including design and writing of the ancillary protocol, analysis, interpretation, and preparation of the report. All authors, with the exception of IH and SM, participated in data collection. SM undertook all analyses. All authors reviewed and helped revise the paper, and approved the submitted version. A list of participating institutions can be found in the webappendix.

See Online for webappendix

Conflicts of interest

KM has received payment for writing the report from Daiichi Sankyo and honoraria from Taiho and Yakult Honsha. NB has received a grant from Taiho; NB's institution has received grants from Taiho. YS has received honoraria from Taiho and Yakult Honsha; YS's institution has received board membership fees and grants from Daiichi Sankyo. AT has received honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha;

AT's institution has received grants from Taiho, Daiichi Sankyo, and Yakult Honsha. SS has received honoraria from Yakult Honsha and lecture fees from Taiho; SS's institution has received grants from Taiho. HB has received board membership fees from Taiho and Daiichi Sankyo, and lecture fees from Taiho, Daiichi Sankyo, Yakult Honsha, and Wyeth; HB's institution has received grants from Taiho, Daiichi Sankyo, Yakult Honsha, Kyowa Hakko Kirin, and Wyeth. TS has received consulting fees from Taiho, honoraria and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Kyowa Hakko Kirin and Wyeth; TS's institution has received grants form Taiho. TD has received honoraria from Taiho, Wyeth, and Yakult Honsha, and lecture fees from Taiho, Daiichi Sankyo, Wyeth, and Yakult Honsha; TD's institution has received grants from Taiho and Yakult Honsha. KI's institution has received grants from Taiho. TN has received honoraria from Taiho, Wyeth, and Yakult Honsha; TN's institution has received grants from Daiichi Sankyo. KY has received lecture fees from Taiho, Daiichi Sankyo, Wyeth, and Yakult Honsha; KY's institution has received grants from Taiho. HT has received board membership fees from Daiichi Sankyo, consulting fees from Yakult Honsha, and honoraria from Taiho and Daiichi Sankyo. TE has received lecture fees from Kyowa Hakko Kirin, Taiho, Wyeth, and Yakult Honsha; TE's institution has received grants from Taiho and Yakult Honsha. ST's institution has received grants from Taiho. HK has received honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha; HK's institution has received grants from Taiho and Daiichi Sankyo. HK's institution has received grants from Daiichi Sankyo. YK has received board membership fees from Daiichi Sankyo, Kyowa Hakko Kirin, Taiho, and Wyeth, and honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha; YK's institution has received grants from Taiho, Daiichi Sankyo, and Yakult Honsha. MW has received board membership fees, honoraria, and lecture fees from Taiho; MW's institution has received grants from Taiho. IH has received board membership fees from Taiho, and consulting fees, honoraria, and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Kyowa Hakko Kirin. SM has received board membership fees from Daiichi Sankyo, consulting fees and honoraria from Taiho and Daiichi Sankyo; SM's institution has received grants from Daiichi Sankyo. KS has received board membership fees from Taiho, honoraria and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Wyeth; KS's institution has received grants from Taiho.

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A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study)

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Abstract

Aims: Clinically serosa-positive (T3–4) gastric cancer has a poor prognosis. This phase II trial explored the feasibility and safety of preoperative chemotherapy followed by D2 or D3 gastrectomy in this type of gastric cancer.
Methods: Patients with T3–4 gastric cancer received one course of S-1 (80 mg/m^2 daily for 3 weeks) and cisplatin (60 mg/m^2 on day 8) chemotherapy and then underwent D2 or D3 gastrectomy with curative intent. Primary endpoint was toxicities.
Results: Of 50 patients enrolled, 49 were eligible and received the treatment protocol. Chemotherapy-related toxicities were mild; grade 3 neutropenia in 2 patients, anorexia in 3, and nausea in 2, and no grade 4 toxicities. Clinical response was achieved in 13 of 34 evaluable patients. Of the 49 patients, 39 underwent D2 or D3 dissection. There was no surgical mortality. Operative morbidity occurred in 5 of 49 patients, including pancreatic fistula in 1 and abdominal abscess in 2.
Conclusion: This multi-modality treatment seems to be feasible and safe for T3–4 gastric cancer.

Keywords: Gastric cancer; Chemotherapy; Surgery; Phase II

Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most frequent malignancy in Japan, South America, and Eastern Europe.[1] Complete resection is essential for cure,[2] and because more than half of T3 and T4 tumors have metastasized to lymph nodes along the major branch arteries or in the para-aortic area, complete resection has involved D2 or D3 dissection in Japan.[3,4] However, despite resection of these tumors with curative intent, prognosis has been limited.[5] To improve the survival of these patients, new treatment strategies must be developed.

Most clinical trials of postoperative adjuvant chemotherapy have failed to prove a survival benefit.[6] However, a large phase III trial recently demonstrated that adjuvant chemotherapy with S-1 (1 M tegafur–0.4 M gimestat–1 M ostat potassium) significantly improved survival after D2 curative

Abbreviations: CF, 5-FU plus cisplatin; ECF, triplet chemotherapy of CF plus epirubicin; DCF, CF plus docetaxel; JACCRO, Japan Clinical Cancer Research Organization; WBC, white blood cell count; PLT, platelet count; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaline phosphatase; RECIST, response evaluation criteria in solid tumors; JCOG, Japan Clinical Oncology Group.

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gastrectomy in Japanese patients with T2N+ or T3 disease.[7] Based on this, D2 surgery and postoperative S-1 chemotherapy has been established as a standard treatment in Japan. Nonetheless, even with adjuvant S-1 chemotherapy, the prognosis for T3 tumors was not satisfactory.

Preoperative chemotherapy followed by extended surgery has some theoretical benefits when compared with postoperative chemotherapy.[8] If bulky tumors are reduced in size by chemotherapy, complete tumor removal could theoretically be easily achieved by extended surgery. If distant micrometastases are eliminated by chemotherapy, complete resection by extended surgery may improve survival and result in cure in some cases. However, preoperative chemotherapy followed by extended surgery has not been confirmed in phase III trial.

A high response rate and relatively low toxicity are required for preoperative chemotherapy, because target tumors are resectable or marginally resectable and the patients must receive potentially curative surgery after chemotherapy. Combined chemotherapy with S-1 plus cisplatin is an attractive regimen for preoperative chemotherapy for gastric cancer. A previous phase II trial of this regimen in metastatic gastric cancer reported a high response rate of 76% and acceptable toxicities.[9] Recently, a Japanese phase III trial of chemotherapeutic regimens for metastatic gastric cancer (SPIRITS trial) demonstrated that S-1 plus cisplatin led to significantly longer median overall survival than S-1 alone (13 months vs. 11 months).[10] Moreover, in the recent international phase III trial (FLAGS), S-1 plus cisplatin had lower toxicity but achieved equally overall survival compared with 5-FU plus cisplatin (CF) (Ajani JA, et al. presented at the 2009 Gastrointestinal Cancers Symposium). Triplet chemotherapy of CF plus epirubicin (ECF) or CF plus docetaxel (DCF) is effective but more toxic than CF.[11]

However, the influence of preoperative chemotherapy on D2 or D3 surgery has not been fully evaluated, although D2 and D3 gastrectomy are safe procedures in Japan.[12] Unlike D0 or D1 surgery, D2 or D3 gastrectomy involves nodal dissection along the pancreas, which can cause pancreatic fistula or abdominal abscess. These complications can be lethal and might be increased by preoperative chemotherapy. The effect of preoperative chemotherapy on surgical mortality or morbidity with these procedures has not been fully clarified. Recently, preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 dissection was tested in phase II trial to evaluate the efficacy and toxicity in Japan.[13] However, this trial has been terminated due to high treatment-related death during the accrual. A safe and effective regimen before extended surgery has yet to be reported.

The Japan Clinical Cancer Research Organization (JACCRO) therefore, conducted a multi-institutional phase II trial (JACCRO GC-01) to evaluate the feasibility and safety of preoperative chemotherapy with S-1 plus cisplatin followed by curative D2 or D3 gastrectomy for clinically serosa-positive (T3–4) gastric cancer.

Patients and methods

Eligibility criteria

Eligibility criteria were: (1) histologically proven gastric adenocarcinoma; (2) stage clinically assessed as T3–4, N0–N3 which is classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma,[14] and M0; (3) age 20–75 years; (4) Eastern cooperative oncology group (ECOG) performance status 0–1; (5) no prior therapy; (6) sufficient organ function [white blood cell count (WBC) 4000–12,000 mm^3, platelet count (PLT) >100,000/mm^3, glutamic oxaloacetic transaminase (GOT) <80 IU/l, glutamic pyruvic transaminase (GPT) <80 IU/l, total bilirubin <1.5 mg/dl, alkaline phosphatase (ALP) < two times greater than upper limit of normal, creatinine <1.2 mg/dl, creatinine clearance >60 ml/min, and hemoglobin >8.0 g/dl]; and (7) written informed consent. Clinical diagnosis was based on gastric fiberscopy, upper gastrointestinal series, computed tomography, and ultrasonography. Serosal invasion of the primary tumor was evaluated by computed tomography. Endoscopic ultrasonography or diagnostic laparoscopy was not mandatory, because these remain outside of routine preoperative examinations in Japan. Exclusion criteria were (1) severe co-morbidities; (2) active and acute bleeding from the digestive tract; (3) insufficient oral intake; (4) synchronous or previous malignancy other than carcinoma *in situ*; and (5) contraindications to S-1 or cisplatin. All patients provided informed consent before registration and were registered centrally at the JACCRO Data Center by means of the online Flexible licence assisted data server (FLADS) system. The JACCRO Data Center conducted the data management, central monitoring, and statistical analysis.

Preoperative chemotherapy

On the basis of previous reports S-1 (80 mg/m^2) was given orally every day for 3 weeks and cisplatin (60 mg/m^2) was administered intravenously on day 8 as one course.[9,10] If the patient had a WBC of 2000/mm^3 or lower, neutrophil count of 1000/mm^3 or lower, PLT of 75,000/mm^3 or lower, diarrhea or mucositis of grade 3 or higher, GOT or GPT of grade 2, or serum creatinine of grade 1, chemotherapy was postponed until recovery from these adverse events and the next dose of S-1 was reduced to 70 mg/m^2. For diarrhea or mucositis of grade 1, chemotherapy was postponed until recovery. In the case of GOT and/or GPT of grade 3 or higher or serum creatinine of grade 2 or higher, chemotherapy was terminated. If the patient had cardiac or neurologic toxicities, chemotherapy was postponed until recovery from these toxic effects and confirmation of their cause. For any other adverse events of grade 2 or higher, chemotherapy was postponed until recovery. If the chemotherapy was postponed but the toxicities had not resolved within 21 days, the chemotherapy was terminated after this period.

Surgery

Tumor resectability was assessed after completion of chemotherapy. Resection criteria were (1) R0 resection was anticipated by D2 or extended D2 gastrectomy; (2) sufficient organ function (WBC $>3000/mm^3$, neutrophils $>1000/mm^3$, PLT $>100{,}000/mm^3$, GOT <100 IU/l, GPT <100 IU/l, creatinine <1.5 mg/dl); and (3) no active infection. Patients who fulfilled these criteria were treated by D2 or D3 gastrectomy with curative intent between two and four weeks after finishing chemotherapy. The precise procedure of D2 and D3 dissection has been reported previously.[12,15] Combined resections of adjacent organs were permitted when these procedures were indispensable for curative resection.

Treatment defined by the protocol

The treatment protocol was defined as completed when a patient received preoperative chemotherapy and underwent R0 resection by gastrectomy with D2 or D3 dissection. The treatment protocol was stopped when: (1) response was evaluated as progressive disease during chemotherapy; (2) the patient did not meet the criteria for surgery after chemotherapy; (3) the patient underwent surgery after chemotherapy but this took the form of exploratory laparotomy, bypass, or non-R0 resection; (4) the patient refused further participation; or (5) the doctor recommended stopping the protocol. After the treatment protocol was stopped, any treatment was allowed and postoperative adjuvant therapy was not defined.

Endpoints

Primary endpoint was toxicities. Secondary endpoints included response rate and overall survival.

Evaluation

The response rate was evaluated only in patients with measurable lesions; Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used[16] and response to chemotherapy was evaluated by external review committee. Adverse reactions during chemotherapy were evaluated by National Cancer Institute – Common Toxicity Criteria Version 2.0.[17]

Statistical hypothesis

As it is difficult to predict the occurrence of severe adverse events or treatment-related deaths and to calculate sample size, feasibility and safety was evaluated in calculated sample size based on the response rate to be required in this setting. A Simon optimal two-stage design[18] was used to calculate the sample size, assuming an anticipated response rate of 50% and a threshold response rate of 30% with 10% alpha error and 10% beta error. Using this design, if at least 8 objective responses were observed among 22 patients in the first stage, an additional 24 patients would be recruited to the second stage. Taking into account tumors without measurable lesions and patients not fulfilling the eligibility criteria, sample size was determined to be 50. Statistical analysis was performed with SAS version 9.1 (SAS Institute, Cary, NC). This phase II trial was approved by the JACCRO Protocol Review Committee and the institutional review board of each of the 8 JACCRO institutions involved.

Results

Patients

Between February 2004 and January 2005, 50 patients were enrolled and the study was terminated. During the accrual, unpredicted severe adverse events or treatment-related death was not observed. One of these patients declined to participate, while the other 49 were eligible and received the treatment protocol. Table 1 shows patient demographics and tumor characteristics. Clinically apparent nodal disease was observed in 40 patients.

Preoperative chemotherapy and toxicities

Of all 49 eligible patients, 3 did not receive cisplatin because of S-1-related toxicity. The average proportion of actual dose to proposed dose was 94% (2219.2 mg/2348.6 mg) for S-1 and 94% for cisplatin (87.8 mg/

Table 1
Patient demographics and pre-treatment tumor characteristics (all eligible patients, $n = 49$).

Age (median, range)	62, 20–73
Sex (male/female)	36/13
PS (0/1)	46/3
Macroscopic type	
1	4
2	6
3	24
4	14
5	1
Histologic type	
Differentiated	17
Undifferentiated	31
Miscellaneous	1
Depth of tumor invasion	
T3	44
T4	5
Nodal status[a]	
N0	9
N1+, perigastric	17
N2+, along major branch arteries	12
N3+, para-aortic	11

[a] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]

92.0 mg). Adverse events during chemotherapy are shown in Table 2. There were no grade 4 and a few grade 3 toxicities.

Clinical response

Clinical response could be evaluated in 34 patients who had enlarged lymph nodes as target lesions as defined by RECIST criteria. There were 13 responders (all showed partial response); 18 patients had stable disease and 3 had progressive disease. Thus, 13 of 34 evaluable patients demonstrated a clinical response (38%) with a 95% confidence interval from 22% to 56%.

Surgery

All of the 49 patients who completed chemotherapy underwent surgery. Surgical findings are shown in Table 3. Three patients underwent exploratory laparotomy due to massive peritoneal dissemination, and 7 underwent palliative D0 or D1 resection due to peritoneal dissemination or extended lymph node metastasis. Curative resection was intended for the remaining 39 patients; D2 was performed in 27 and D3 in 12. Thus, D2 or D3 was performed in 39 of all eligible 49 patients. Consequently, R0 resection was performed in 38 patients, R1 in 1 due to positive peritoneal cytology, and R2 in 7 due to peritoneal dissemination or extended lymph node metastases (Table 3). Thus, the proportion of R0 resections was 78% (38 of all eligible 49 patients), with a 95 per cent confidence interval from 66% to 89%.

Surgical morbidity and mortality

Surgical complications are shown in Table 4. There was no operative mortality. On the other hand, operative morbidity was observed in 5 of the 49 patients including pancreatic fistula in 1 and abdominal abscess in 2. No anastomotic leakage was observed and no patients required re-operation for morbidity.

Table 2
Adverse events during chemotherapy in all eligible patients ($n = 49$).

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	48	0	1	0	0
Neutrophils	38	4	5	2	0
Hemoglobin	40	7	2	0	0
Platelets	48	0	1	0	0
Total bilirubin	48	1	0	0	0
GOT	46	2	1	0	0
GPT	47	1	1	0	0
ALP	46	3	0	0	0
BUN	45	0	4	0	0
Urine creatinine	47	1	1	0	0
Urine protein	47	1	1	0	0
Anorexia	33	8	5	3	0
Nausea	37	6	4	2	0
Vomiting	42	3	4	0	0
Diarrhea	45	3	1	0	0
Pigmentation	45	3	1	0	0

Table 3
Surgical findings in all operated patients ($n = 49$).

Type of surgery	
Proximal gastrectomy	1
Distal gastrectomy	18
Total gastrectomy	27
Exploratory laparotomy	3
Dissection ($n = 46$)[a]	
D0	4
D1	3
D2	27
D3	12
Combined resection	
Spleen	13
Pancreas	4
Gall bladder	8
Spleen + pancreas	2
None	22
Operation time (minutes)	
Median, range	232, 25–590
Blood loss (ml)	
Median, range	342, 0–2760

[a] Three missing cases were exploratory laparotomy.

Pathological response

Details of pathological data are shown in Table 5. A total of 18 patients were diagnosed as pathological T1 or T2 disease. The pathological response rate in resected patients, defined by the degeneration/necrosis area $\geq 1/3$, was 39%. On the other hand, nodal status, which was classified by 2nd English Edition of Japanese Classification of Gastric Carcinoma, was evaluated in 39 patients who underwent D2 or D3 gastrectomy. Pathological N0 was observed in 8 patients.

Overall survival

Survival time was estimated in all 49 patients who were eligible. Median follow-up period was 31 months from 27 to 38 months. The overall survival curve is shown in Fig. 1. The three-year survival rate was 43.0% with a 95% confidence interval from 35.6% to 50.3%.

Discussion

This multi-institutional phase II prospective trial demonstrated neither treatment-related death nor severe adverse

Table 4
Surgical complications in all operated patients ($n = 49$).

	Number of patients	%
Anastomotic leakage	0	0
Pancreatic fistula	1	2
Abdominal abscess	2	4
Pneumonia	0	0
Ileus	0	0
Wound infection	1	2
Renal dysfunction	1	2

Table 5
Pathological results.

Depth of tumor invasion ($n = 46^a$)			
T1		3	
T2		15	
T3		19	
T4		9	
Nodal status[b] ($n = 39^c$)			
	D2	D3	D2/D3
N0	7	1	8
N1	12	3	15
N2	6	4	10
N3	2[d]	4	6

[a] Three missing cases were exploratory laparotomy.
[b] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]
[c] Ten missing cases included exploratory laparotomy in 3, palliative D0 in 4 and palliative D1 gastrectomy in 3.
[d] Two cases were determined by a few lymph nodes of N3 dissected in addition to D2 dissection.

events by preoperative chemotherapy of S-1 plus cisplatin followed by extended surgery, suggesting that this multimodality treatment was safe and feasible.

Surgical mortality

No operative mortality was observed in the study, although 39 of the 49 patients underwent D2 or D3 surgery after preoperative chemotherapy. In the Japan Clinical Oncology Group (JCOG) 9501 phase III trial that compared D2 and D3 resections, mortality rate was reported to be 0.8% in both arms.[12] Thus, our results suggested that mortality of D2 or D3 was not increased by preoperative chemotherapy with S-1 plus cisplatin. In the retrospective study evaluating the feasibility and safety of preoperative chemotherapy of S-1 plus cisplatin followed by D2 dissection, no operative mortality was reported.[20,21] In the MAGIC phase III trial comparing surgery alone versus pre- and postoperative chemotherapy combined with surgery for resectable gastric cancer, operative mortality was 5.6% in the chemotherapy group

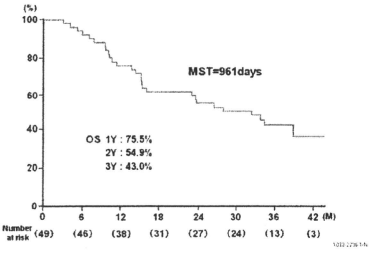

Figure 1. Overall survival ($n = 49$). Median survival time was 31.5 months. Overall survival was 75.5% at 1 year, 54.9% at 2 years, and 43.0% at 3 years.

and 5.9% in the surgery group, suggesting that mortality did not increase by preoperative chemotherapy (with an ECF regimen).[19] However, in that trial, most patients underwent less than D2 surgery. On the other hand, in JCOG 0001 trial evaluating the efficacy and safety of preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 surgery, operative mortality was observed in 2.0%.[13] Thus, operative mortality may depend on the toxicity of the preoperative chemotherapy and the extent of the lymph node dissection.

Pancreas-related surgical morbidity

Pancreatic fistula is the major specific complication after D2 or greater extended surgery. In this study, pancreatic fistula was observed in 1 patient and abdominal abscess in 2 patients. As no apparent anastomotic leak was found in the latter 2 patients, the abdominal abscess might have been caused by pancreatic fistula. Thus, pancreatic fistula might have been a complication in a maximum of 3 of 49 patients in the present study, a proportion almost equivalent to that found in the JCOG 9501 phase III trial.[12] In that trial, tumors were diagnosed as T2–T4, N0–N2, and P0 by surgical findings.[12] In the present study, on the other hand, all tumors were clinically diagnosed as T3–T4. Moreover, 11 of the present patients had clinically apparent N3 disease. Hence, although the tumors were more advanced in this study, the rate of pancreatic fistula was not increased by preoperative chemotherapy with S-1 plus cisplatin. On the other hand, pancreatic fistula was observed in 12.2% in JCOG 0001 trial consisting of CPT-11 plus cisplatin followed by D3 dissection.[13] Toxic regimen could increase the rate of pancreatic fistula.

Overall surgical morbidity

In the present study, overall surgical morbidity was 5 of 49 which was slightly lower than the 20.9% to 28.1% observed in the JCOG 9501 trial.[12] In particular, anastomotic leakage and re-operation were not observed in this study, while rates of these events were 1.9% and 2.7%, respectively, in the JCOG 9501 study.[12] Thus, operative morbidity did not increase with the present preoperative chemotherapy regimen. In the MAGIC trial, morbidity was similar in both arms of the trial; 45.3% in the surgery alone group and 45.7% in chemotherapy group.[19] Because our preoperative chemotherapy was performed only short term, operative morbidity appears not to increase even after D2 or D3 surgery.

Chemotherapy-related toxicities

Chemotherapy-related toxicities were relatively mild in this study. There were no grade 4 toxicities and only a few grade 3 toxicities including neutropenia, anorexia, and nausea. In the SPIRITS trial,[10] grade 3/4 bone marrow suppression was more frequently observed when compared with the present trial. Chemotherapy was limited to one course in this study while it continued until disease

progression in the SPIRITS trial, which would explain the difference in the toxic profile between the two studies. Our results may also suggest that mild toxicities led to high compliance with this chemotherapy regimen and low morbidity and mortality of D2 or D3 resection.

Response to the chemotherapy

The present study achieved a relatively high response rate of 38%, which was almost the same as observed in the pathological response of the primary tumor. Previous trials in metastatic gastric cancer have demonstrated that response rate was 76% in a phase II trial[9] and 54% in the SPIRITS phase III trial.[10] The response rate in this study was slightly lower, which may be attributable to only one course of chemotherapy being administered in the present study. In the MAGIC phase III trial, three courses of ECF chemotherapy were performed preoperatively.[19] Considering the low toxicities of one course of S-1 plus cisplatin and the low mortality and morbidity of subsequent extended surgery, an additional two or three courses of this chemotherapy should be evaluated in another phase II study.

Survival

In the present study, all patients were clinically diagnosed with T3 or T4 disease before entry and overall 3-year survival rate was 43.0%. It has been reported that clinical diagnosis of T3–T4 was accurate in 74.4% in clinical T3 tumors and 87.0% in clinical T4 tumors.[5] M0 was evaluated by computed tomography and diagnostic laparoscopy was not mandatory in this study, therefore, peritoneal metastases may not be excluded in this series.[22] Retrospective analyses of Cancer Institute Hospital of Japan have reported 5-year survival rates of 25.3% and 1.8% in pathological T3 and T4 with any N, respectively.[5] In this series of patients, the 3-year survival rate was 43% despite that R0 resection was only performed in 77.6%. Although it may be difficult to compare these survival rates, our results appear to be worthy of further investigation using the same strategy.

Conclusion

In conclusion, preoperative chemotherapy with one course of S-1 plus cisplatin followed by gastrectomy with D2 or D3 dissection seems to be feasible and safe for clinically serosa-positive (T3–4) gastric cancer.

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Conflict of interest

No authors have any conflict of interest.

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Recent Advances in Chemotherapy for Advanced Gastric Cancer in Japan

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Abstract
In the early 1990s, a combination of 5-fluorouracil (5-FU) and cisplatin was widely adopted to treat advanced gastric cancer; however, no survival advantage over single-agent 5-FU was confirmed by the results of randomized trials conducted over a long period. Recently developed agents such as irinotecan, taxanes (docetaxel), and new oral fluorouracil (S-1) have yielded more promising results, with a response rate of over 50% and a median survival time of over 10 months in combination studies. These newer combination regimens were investigated in various randomized phase III studies to clarify if the newer-generation regimens provided a survival advantage over the older-generation regimens. Based on the findings of a large randomized study, S-1 has become standard in the adjuvant setting after D2 dissection curatively resected stage II and III gastric cancer. This article reviews the recent advances in gastric cancer chemotherapy, especially in Japan.

Key words Gastric cancer · Chemotherapy · Standard chemotherapy

Introduction

Gastric cancer (GC) is the most common malignancy in Japan. In 1998, more than 100000 new cases were reported[1] and by 2015, it is anticipated that this number will have climbed to nearly 150000.[2] The only potentially curative treatment for GC is surgical resection of all of the gross and microscopic disease; however, recurrence is common, both in regional and distant sites. The standard treatment for advanced or relapsed gastric cancer (AGC) is chemotherapy, aimed at prolonging survival.

Until about 10 years ago, there were few medical oncologists in Japan, and gastrointestinal surgeons played the part of oncologists in designing cancer chemotherapy for patients with gastric or colorectal carcinomas. The educational systems for medical oncologists were initiated by the Japan Society of Medical Oncology (JSMO). However, from 2005 to 2007 only 205 specialists in medical oncology passed the JSMO examination. The JSMO predicts that 80 medical oncologists will be initiated into the system each year, but this will be insufficient to cover all patients who have AGC. Thus, surgeons must continue to treat their patients with AGC oncologically in Japan. Our aim in writing this review is to make surgeons aware of the widely used regimen or standard chemotherapy for GCs, because we expect them to be able to treat their AGC patients effectively and safely.

Anticancer Drugs for AGC

One of the most widely studied single-agent chemotherapies is the antimetabolite, 5-fluorouracil (5-FU), which confers response rates of approximately 20%.[3,4] Tumor antibiotics (mitomycin C, doxorubicin, and epirubicin), heavy metals (cisplatin and carboplatin), taxanes (paclitaxel and docetaxel), and camptothecins (irinotecan and topotecan) have also been evaluated in the treatment of AGC and afford response rates ranging from 5% to 30%.[5–7] Newer fluorinated pyrimidines such as the 5-FU prodrug, UFT (uracil and tegafur), and 5-FU derivatives such as S-1, are of particular interest since they can be administered orally and allow for mimicking of conventional infusional therapy.

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Is Chemotherapy Effective Against AGC?

Several combination chemotherapeutic regimens have been evaluated for their efficacy and tolerability in the treatment of AGC. They often achieve adequate response rates with variable toxicity in previously untreated AGC patients. Compared with the best supportive care, the median survival with combination chemotherapy appears to be increased by 2 months or longer.[8,9]

Standard Chemotherapy for AGC in Western Countries

In Western countries, FAM (5-FU/adriamycin/mitomycin C), FAMTX (5-FU/adriamycin/methotrexate), ELF (etoposide/leucovorin/5-FU), and CF (cisplatin/5-FU) regimens have been compared in several studies. In consideration of their moderate activity, we do not recommend that any of the evaluated regimens be regarded as the standard treatment. In a prospective, randomized phase III study, Waters et al.[10] compared a combination of epirubicin, cisplatin, and 5-FU (ECF) with FAMTX in previously untreated patients with AGC. This ECF regimen resulted in significantly higher response rates (46% vs 21%), median survival (8.7 vs 6.1 months), and 2-year survival rates (14% vs 5%), and is the de facto standard treatment for AGC in Europe.

In a randomized phase III study (TAX325), Moiseyenko et al.[11] compared the efficacy and safety of cisplatin and 5-FU (CF) vs docetaxel, cisplatin, and 5-FU (TCF) as front-line therapy in patients with metastatic or nonresectable AGC. The final analysis revealed that the addition of docetaxel to CF resulted in significantly higher response rates (37% vs 25%, for TCF and CF, respectively). Time-to-progression, the primary study endpoint, was significantly higher in the TCF-treated patients than in the CF-treated patients (5.6 months vs 3.7 months, respectively; $P < 0.0004$). At the time of this interim analysis, the observed difference in median overall survival favored TCF over CF (9.2 vs 8.6 months, respectively; $P = 0.0201$). The common severe toxicities associated with TCF and CF included stomatitis (20.8% and 27.2% of subjects, respectively), lethargy (21.3% and 17.9%), diarrhea (20.4% and 8.0%), nausea (15.8% and 18.8%), vomiting (14.9% and 18.8%), and febrile neutropenia or neutropenic infection (30% and 13.5%). Based on the results of the TAX325 trial, TCF is regarded as standard chemotherapy in the United States.

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Until the early 1990s there was no standard chemotherapy in Japan, although 5-FU infusion, CF, and uracil-tegafur, and mitomycin C (UFTM) regimens were widely employed in the clinical setting. In a three-arm, large randomized phase III trial, Ohtsu et al.[12] compared 5-FU with CF and with UFTM. They found 5-FU to be equal to or better than UFTM in terms of response and survival. Although CF achieved a better response rate and progression-free survival (PFS) than 5-FU monotherapy, there was no difference in overall survival between these two arms (7.3 and 7.1 months for CF and 5-FU, respectively). 5-FU monotherapy remained as a reference arm in the next phase III trial of the JCOG group.

New Anticancer Agents

S-1 consists of a 1:0.4:1 molar ratio mixture of tegafur and two 5-FU-modulating substances: gimeracil (5-chloro-2,4-dihydroxypyrimidine, CDHP) and oteracil (potassium oxonate). Sakata et al.[13] investigated the efficacy of S-1 as a single chemotherapeutic agent in AGC patients in a late phase II study. Four cycles of S-1 were administered twice a day to 51 patients at a dose of 80 mg/m^2 per day. One complete response (CR) and 24 partial responses (PRs) were observed, with an overall response rate of 49%. The median survival time (MST) achieved by S-1 in a phase II study was 8 months and it was generally well tolerated, the major toxicities including anemia, leukopenia, granulocytopenia, diarrhea, malaise, and proteinuria.

Boku et al.[14] reported a phase II trial of cisplatin/CPT-11 combination chemotherapy involving 44 patients with AGC by the JCOG. Cisplatin was administered at a dose of 80 mg/m^2 on day 1, and CPT-11 was administered at a dose of 70 mg/m^2 on days 1 and 15 every 4 weeks. They reported 1 CR and 20 PR, with an overall response rate of 48.0%, and an MST of 9 months. The grade 4 major toxicities with this combination were leukopenia (9.0%), neutropenia (57.0%), thrombocytopenia (2.0%), and anemia (5.0%).

JCOG 9912 Trial

The JCOG conducted another three-arm, randomized phase III trial in 1999 (the JCOG 9912 trial), evaluating the superiority of cisplatin/CPT-11 over the reference arm 5-FU, and the noninferiority of S-1 to 5-FU. The MSTs achieved by 5-FU, cisplatin/CPT-11, and S-1 were 10.8 months, 12.3 months, and 11.4 months,

respectively. Survival was not significantly better with cisplatin/CPT-11 vs 5-FU ($P = 0.055$); however, the non-inferiority of S-1 vs 5-FU was confirmed ($P < 0.001$). Subsequently, S-1 has been widely used in Japan as the standard and first-line chemotherapy for AGC.

Combination Chemotherapy with S-1

The efficacy of combination chemotherapy with S-1 in AGC has been assessed in a number of phase I/II studies. Cisplatin at a dose of 60 mg/m^2 on day 8 was combined with S-1 for 3-weeks-on and 2-weeks-off.[15] Treatment was repeated every 5 weeks, unless disease progression was observed. The subjects of this trial were 19 AGC patients, and the incidences of severe (grade 3/4) hematological and nonhematological toxicities were 15.8% and 26.3%, respectively, but all cases were manageable. The response rate was 74% (14/19; 95% confidence interval, 54.9–90.6), and the MST was 383 days.

Komatsu et al.[16] reported the results of a phase I/II study with CPT-11 and S-1 (IRIS) in AGC patients. S-1 was given orally twice a day for 14 days, and CPT-11 was administered as a 90-min intravenous infusion on days 1 and 15. This regimen was repeated every 4 weeks. Fifteen patients were registered in the phase I study and 9 were added to the phase II study. Most of the nonhematological toxicities were classified as grade 2 or lower, except for grade 3 nausea and grade 3 level 2 dermatitis. The hematological toxicities consisted of grade 4 neutropenia in one patient at level 1 and level 2 in phase I, and grade 4 neutropenia in 4 patients at level 2 in phase II. All of these patients recovered after the drug was suspended. These side effects were tolerable, and the overall response rate was 54.2%. The MST achieved with this regimen was 581 days.

Yoshida et al.[17] performed a phase I study and a phase II study of docetaxel in combination with S-1 in patients with AGC. In the phase I study, neutropenia and leukocytopenia were the dose-limiting toxicities (DLTs). The recommended dose (RD) was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 3 weeks. In the phase II study, the response rate was 52.1% and the MST was 434 days. The most common severe toxicities were neutropenia (18.5%), leukopenia (12.3%), anemia (2.6%), stomatitis (10.4%), anorexia (6.3%), and nausea (6.3%). Yamaguchi et al.[18] reported a phase I/II study of docetaxel in combination with S-1. During dose escalation, G3 infection without neutropenia was the DLT. The RD was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 4 weeks. The response rate was 45.7%, the MST was 14.2 months, and the PFS was 4.3 months. The most common severe toxicities were neutropenia (67.4%), leukopenia (41.3%), anemia (21.7%), anorexia (21.7%), nausea (6.5%), and stomatitis (6.5%).

Phase III Trials of S-1 Monotherapy vs S-1 in Combination

Based on the results obtained in the above phase II studies, three large randomized phase III studies, the SPIRITS trial, the TOP-002 trial, and the JACCRO GC03 trial, were conducted independently to compare data with that of S-1 monotherapy. In the SPIRITS trial,[19] chemotherapy-naïve patients with AGC were randomly assigned to receive either S-1 plus cisplatin or S-1 alone. In the patients assigned to receive S-1 plus cisplatin, the S-1 (40–60 mg depending on the patient's body surface area) was given orally, twice daily for 3 consecutive weeks, and 60 mg/m^2 cisplatin was given intravenously on day 8, followed by a 2-week rest period within a 5-week cycle. Patients assigned to receive S-1 alone were given the same dose of S-1 twice daily for 4 consecutive weeks, followed by a 2-week rest period, within a 6-week cycle. The primary endpoint was overall survival and the secondary endpoints were PFS, proportion of responders, and safety. Of the 305 patients enrolled, 7 were ineligible or withdrew consent, 148 patients were assigned to the S-1 plus cisplatin group, and 150 were assigned to the S-1 alone group. Median overall survival was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (13.0 vs 11.0 months, respectively; hazard ratio, 0.77; 95% confidence interval, 0.61–0.98; $P = 0.04$). The PFS was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (median PFS, 6.0 months vs 4.0 months, respectively; $P < 0.0001$). Moreover, of the 87 patients with target tumors, assigned to receive S-1 plus cisplatin, 1 showed a CR and 46 showed a PR (total response rate, 54%), and of the 106 patients with target tumors, assigned to receive S-1 alone, 1 showed a CR and 32 showed a PR (total response rate, 31%). Grade 3 or 4 adverse events including leukopenia, neutropenia, anemia, nausea, and anorexia were reported in the group assigned to S-1 plus cisplatin rather than in the group assigned to S-1 alone. There were no treatment-related deaths in either group. Based on this trial, S-1 plus cisplatin became regarded as a new standard first-line treatment for patients with AGC in Japan.

A randomized phase III trial was conducted to evaluate the efficacy and safety of IRIS (S-1/CPT-11) vs S-1 for AGC.[20] Patients with previously untreated AGC were randomized to Arm A (oral S-1, 80 mg/m^2 on days 1–28, every 6 weeks) or Arm B (IRIS: oral S-1,

80 mg/m^2 on days 1–21; and intravenous irinotecan, 80 mg/m^2 on days 1 and 15, every 5 weeks) by dynamic allocation. Treatment was continued unless disease progression or unacceptable toxicity was observed. The primary endpoint was overall survival and the secondary endpoints were 1-year survival, response rate, and toxicity. As a result, 326 patients were randomized to Arm A (162 patients) or Arm B (164 patients), with a final 315 evaluable patients (160 in Arm A and 155 in Arm B). The patients' characteristics were well balanced in the two groups. By the end of the trial, 247 events (78%) had been observed. Although the MST of the Arm A patients was 318 days (95% confidence interval, 286–395) and that of the Arm B patients was 389 days (95% confidence interval, 324–458), Arm B did not show significant superiority to Arm A (log-rank test P = 0.23; hazard ratio = 0.86). The 1-year survival rates were 44.9% in Arm A and 52.0% in Arm B. The response rates were significantly different, being 26.9% in Arm A vs 41.5% in Arm B (chi-square test; P = 0.035) in 187 RECIST (Response Evaluation Criteria In Solid Tumors) evaluable patients. The most common grade 3/4 toxicities in Arm A vs Arm B were neutropenia (10.6% vs 27.1%), diarrhea (5.6% vs 16.1%), anorexia (18.8% vs 17.4%), nausea (5.6% vs 7.1%), and vomiting (1.9% vs 3.2%). Based on this trial, IRIS achieved MST and was better tolerated; however, IRIS did not show significant superiority to S-1 alone in terms of the overall survival. Thus, IRIS could not become a first-line treatment for AGC.

A randomized phase III study comparing S-1 alone with the S-1/docetaxel combination is ongoing through the JACCRO GC03 trial.[21] This study is a prospective, multicenter, multinational (Korea and Japan), nonblinded, randomized, phase III study of patients with AGC. Patients are randomly assigned to receive 3-week cycles of Treatment Arm A (docetaxel and S-1) or 6-week cycles of Treatment Arm B (S-1 only). The primary objective of the study is to compare the median overall survival of the test arm (docetaxel and S-1) with that of the control arm (S-1 only) in patients with AGC. The secondary objectives are to assess the time to tumor progression (TTP), defined as the time from randomization to the date of first documentation of progressive disease (PD); to determine the clinical response (RR = response rate), defined as the sum of the CR and PR according to the RECIST; and to evaluate the safety of the two regimens. It was expected that 628 patients (314 in each treatment arm) would be enrolled in this trial and this has been exceeded, with 628 patients from 103 centers confirmed in September 2008. The first author of this review is a principal participating investigator in this trial, the results of which will be available in 2010.

Future Perspectives of Standard Chemotherapy

If the results of the S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC. A triplet of the S-1/cisplatin/docetaxel combination is expected as the next candidate of the standard regimen.[22] The replacement of heavy metals from cisplatin to oxaliplatin in the combination with S-1 is also expected. Some molecular target agents have already been investigated for AGC. These agents of the new generation are expected to make revolutionary progress in chemotherapy for unresectable or recurrent GCs.

Second-Line Chemotherapy

Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy, but there is no established regimen for patients with AGC failing to respond to, or with progression after, first-line chemotherapy. Although there are some phase III studies ongoing, the treatment of S-1 refractory GC remains controversial with regard to whether S-1 should be continued as a second-line. After the successful adjuvant S-1 results (ACTS-GC trial),[23] the same problem will arise in patients receiving adjuvant S-1 for recurrence. The JACCRO GC05 trial is a randomized phase II/III trial of second-line chemotherapy comparing CPT-11 monotherapy with the S-1/CPT-11 combination for S-1 refractory GC. We expect that the results of this study will resolve the controversy.

Neoadjuvant Chemotherapy (NAC)

Japanese surgeons can control N2 lymph node metastasis by standard gastrectomy with D2 dissection. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Tumors with H0, P0, T3, T4, or N3 are most suitable for this therapy. The downstaging of lymph node metastasis of N3 or over to controllable N2 is the main target of NAC. Other distant metastasis, such as hepatic, lung, or peritoneal dissemination, is usually treated by chemotherapy first, and is not a target of NAC. S-1/cisplatin is widely used for the NAC regimen based on the high response rate reported in a phase II trial.[15] Randomized controlled phase III studies are needed in conjunction with accurate staging of the disease by laparoscopy. The results of histopathologic examination of resected materials following preoperative chemotherapy are thought to be an indicator of chemosensitivity in the postoperative adjuvant setting.

As yet, there is no clear evidence of the utility of NAC for GC, but its benefits will be proved soon by randomized controlled trials.

Adjuvant Chemotherapy

Before 2004, no positive results of adjuvant chemotherapy for curatively resected GC were reported. In the United States, the INT-0116 showed that adjuvant chemoradiation prolonged survival and relapse-free survival.[24] However, most of the patients in this study underwent D0 or D1 surgery, whereas only 10% underwent D2 lymphadenectomy. The European MAGIC trial, performed mainly in the United Kingdom, showed that perioperative and postoperative chemotherapy with ECF significantly prolonged overall survival and progression-free survival. In that study, D2 surgery was not the standard procedure, as it is in Japan. Comparisons of adjuvant chemotherapy vs surgery alone after D2 surgery in Japan were not positive.

In 2007, Nakajima et al.[25] reported positive results of adjuvant UFT based on the NSAS GC trial. In this trial, patients with TNM (tumor node metastasis) stage T2 N1-2 GC were randomly assigned to undergo surgery alone or to undergo surgery followed by postoperative UFT 360 mg/m^2 per day orally for 16 months. However, this trial was terminated before the target number of patients had been reached as accrual was slower than expected, with 190 patients registered and 95 randomized to each group. Nevertheless, after a median follow-up of 6.2 years, the overall and relapse-free survival rates were significantly higher in the surgery+chemotherapy group (hazard ratio for overall survival 0.48, $P = 0.017$; hazard ratio for relapse-free survival 0.44, $P = 0.005$). Furthermore, in 2007 Sakuramoto et al.[23] reported the success of adjuvant S-1 chemotherapy in patients with curatively resected GC. Patients with stage II or III GC who underwent gastrectomy with D2 dissection were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 or to undergo surgery only. In the surgery+S-1 group, S-1 was started within 6 weeks after surgery and continued for 1 year. The treatment regimen consisted of 6-week cycles in which, in principle, 80 mg/m^2 of oral S-1 per day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. There were 529 patients assigned to the surgery+S-1 group and 530 patients assigned to the surgery-only group between October 2001 and December 2004. The trial was stopped on the recommendation of independent data and the safety monitoring committee, because the first interim analysis, performed 1 year after enrollment was completed, showed that the surgery+S-1 group had a higher overall survival rate than the surgery-only group ($P = 0.002$). Analysis of follow-up data showed that the 3-year overall survival rate was 80.1% in the surgery+S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the surgery+S-1 group vs the surgery-only group was 0.68 (95% confidence interval, 0.52–0.87; $P = 0.003$). Adverse events of grade 3 or grade 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute), which were relatively common in the surgery+S-1 group, were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%). It was concluded that S-1 is an effective adjuvant treatment for patients who have undergone a D2 dissection for locally advanced GC.

Conclusions

1. The standard regimen now used for AGC in Japan is the S-1/cisplatin combination, and we are awaiting the trial results about S-1/docetaxel combination chemotherapy. If the results of this S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC.
2. Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy after refractory S-1, but there is still no standard second-line regimen until ongoing phase III results are reported.
3. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Downstaging of N3 (or more) lymph node metastasis to controllable N2 is the main target of NAC.
4. The standard chemotherapy for T2 N1-2 GC after D2 dissection is adjuvant UFT, and that for stage II, III GC after D2 dissection is adjuvant S-1.

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Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer

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Abstract. Combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI) has become a standard regimen for advanced or recurrent colorectal cancer. Numerous studies have reported that long-term use of FOLFOX or FOLFIRI leads to better survival for these patients. Thus, control of the toxicity of these drugs may be crucial to prolonging survival. Fucoidan is one of the major sulfated polysaccharides of brown seaweeds and exhibits a wide range of biological activities. In the present study, we analyzed the effect of fucoidan on suppressing the toxicity of anti-cancer drugs. A total of 20 patients with unresectable advanced or recurrent colorectal cancer scheduled to undergo treatment with FOLFOX or FOLFIRI were randomly allocated into a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). Results showed that fucoidan regulated the occurrence of fatigue during chemotherapy. Chemotherapy with fucoidan was continued for a longer period than chemotherapy without fucoidan. Additionally, the survival of patients with fucoidan treatment was longer than that of patients without fucoidan, although the difference was not significant. Thus, fucoidan may enable the continuous administration of chemotherapeutic drugs for patients with unresectable advanced or recurrent colorectal cancer, and as a result, the prognosis of such patients is prolonged.

Introduction

To prolong the survival of patients with unresectable advanced or recurrent colorectal cancer, it is essential to continue effective chemotherapy for as long as possible. Since the introduction of oxaliplatin for use in Japan in April 2005, combination chemotherapy with oxaliplatin plus 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) has become the standard regimen for advanced or recurrent colorectal cancer, and a high response rate has been reported (1-3). However, FOLFOX and FOLFIRI are associated with severe toxicity, such as nausea, vomiting, stomatitis, diarrhea, fatigue, neutropenia, anemia, thrombocytopenia and liver dysfunction. A number of patients discontinue these effective chemotherapies due to toxicity. Thus, the prognosis of patients with unresectable advanced or recurrent colorectal cancer remains low despite advances in chemotherapeutic drugs.

To reduce the toxicity of chemotherapeutic drugs, various types of drugs or dietary supplements have been introduced (4-6). Among these supplements, fucoidan has been reported to exhibit anti-inflammatory, antiviral and anti-tumor activities (7-9). Fucoidan is a sulfated polysaccharide found mainly in various species of brown seaweeds such as kombu, wakame, mozuku and hijiki. Subsequently, fucoidan has become the focus of substantial pharmaceutical research.

The present study investigated whether fucoidan reduces the toxicity of chemotherapeutic drugs in patients with unresectable advanced or recurrent colorectal cancer.

Materials and methods

Patients. Between April 2008 and June 2009, 20 patients were diagnosed with unresectable advanced or recurrent colorectal cancer and were scheduled to undergo FOLFOX or FOLFIRI chemotherapy at our hospital. The Eastern Cooperative Oncology Group performance status of these patients was 0 or 1, and they had adequate bone marrow (platelet count ≥100,000/l, white blood cell count ≥4,000/l, granulocyte count ≥1500/l, hemoglobin level of ≥10.0 mg/dl), renal (serum creatinine concentration ≤2.0 mg/dl), and hepatic (serum bilirubin level ≤2.0 mg/dl) functions. Adjuvant chemotherapy using 5-FU plus LV was administered to 9 of the 20 patients prior to enrollment in this study. The Ethics Committee of Tottori University approved treatment with fucoidan to reduce the toxicity of chemotherapeutic drugs in 2008 (approval no. 1223).

Informed consent was obtained from the 20 patients, who were randomly allocated to a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). The patients were followed up until July 2010. The patient details are shown in Table I.

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Key words: fucoidan, colorectal cancer, chemotherapy, fatigue

Table I. Patient characteristics.

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Age (mean ± SD, years)	71.3±7.5	69.6±8.8	0.762
Male/Female	6/4	7/3	0.639
ECOG			0.653
PS 0/1	5/5	4/6	
Tumor			0.653
Primary/Recurrent	4/6	5/5	
Primary tumor			0.639
Colon/Rectum	6/4	7/3	
Previous chemotherapy			0.653
Yes/No	4/6	5/5	
Site of disease			0.953
Liver	5	4	
Lung	2	2	
Pelvis	1	1	
Peritoneum	1	1	
Lymph node	1	1	
Primary tumor	0	1	

ECOG, The Eastern Cooperative Oncology Group; PS, performance status.

Chemotherapy. A number of versions of FOLFOX therapy exist, of which modified FOLFOX6 (mFOLFOX6) allows for more convenient administration and has been adopted by various medical institutions in association with popularization of outpatient chemotherapy. Thus, mFOLFOX6 has been the first-line therapy for patients with unresectable advanced or recurrent colorectal cancer at our hospital (10). A 2-h intravenous infusion of oxaliplatin (85 mg/m^2) plus l-LV (200 mg/m^2) was followed by a bolus intravenous injection of 5-FU (400 mg/m^2), after which 5-FU (2,400 mg/m^2) was administered by continuous infusion for 46 h. However, 4 of the 20 patients requested FOLFIRI as first-line therapy. In the FOLFIRI regimen, on day 1, 180 mg/m^2 of irinotecan and 200 mg/m^2 of l-LV were administered as a 2-h infusion, prior to a 400 mg/m^2 5-FU intravenous bolus injection. Subsequently, 2,400 mg/m^2 of 5-FU was administered as a 46-h continuous infusion. The duration of one cycle of mFOLFOX6 was the same as that of FOLFIRI (2 weeks). Details of the chemotherapy regimens have been previously described (10).

Fucoidan treatment. Fucoidan is a sulfated polysaccharide that is extracted from brown seaweed, such as mozuku. In the present study, a high-molecular-weight product of fucoidan was used, which was derived from *Cladosiphon okamuranus* (Okinawamozuku) by Marine Products Kimuraya Co., Ltd. (Tottori, Japan). In the fucoidan group, each patient received 150 ml/day of liquid that contained 4.05 g fucoidan for 6 months from the initial day of chemotherapy.

Table II. Major adverse events.[a]

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Leukocytopenia	1	0	0.305
Neutropenia	3	4	0.639
Anemia	2	1	0.531
Thrombocytopenia	0	2	0.136
Nausea	1	1	1.000
Diarrhea	1	2	0.531
Stomatitis	3	1	0.264
Fatigue	1	6	0.019
Peripheral neuropathy	3	5	0.361
Liver dysfunction	0	2	0.136

[a]Adverse events ≥2.

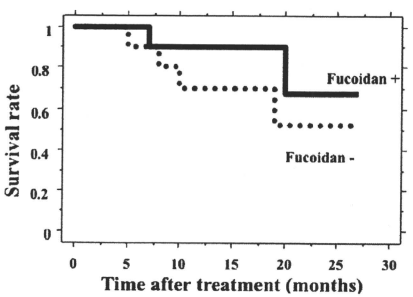

Figure 1. Survival curves of advanced or recurrent colorectal cancer patients. Solid line, survival curve of 10 patients who received fucoidan treatment. Dotted line, survival curve of 10 patients who did not receive fucoidan treatment. The difference was not significant (P=0.314).

Clinical assessment. All toxicities, with the exception of peripheral neuropathy, were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) (11). Peripheral neuropathy was graded according to the specific grading system (12). Hematological variables and clinical status were recorded every 2 weeks during the chemotherapy period. The drug dose level was reduced in the case of severe or persistent toxicity according to our protocol (10). In the case of persistent grade 3 toxicity or when grade 4 toxicity was recorded, chemotherapy was terminated.

Endpoints. The incidence and severity of adverse events were assessed as the primary endpoints, and patient survival, measured from the date of the first treatment until the patient succumbed to the disease, was assessed as the secondary endpoints.

Statistical analysis. The Chi-square test for independence, Fisher's exact probability test and the Mann-Whitney U test were used to compare patient characteristics, treatment status,

adverse events and the anti-tumor effect. The survival rates of the two groups were estimated by the Kaplan-Meier method, and the statistical differences between survival curves were examined by the log-rank test. $P<0.05$ was considered to be statistically significant.

Results

It was noted that fucoidan exhibited no side effects, such as allergic dermatitis. All 20 patients completed the 6 months of fucoidan therapy safely. Additionally, no patients succumbed due to chemotherapeutic toxicity. A total of 307 cycles of mFOLFOX6 or FOLFIRI were administered during the study, with a median of 15.4 cycles per patient (range 7-38). The average number of treatment cycles (19.9) in the fucoidan group was significantly greater than that in the control group (10.8 cycles, $P=0.016$).

The observed toxicities of the chemotherapeutic drugs are listed in Table II. No patients presented with severe toxicity (grade 4) in either group. The occurrences of diarrhea and neurotoxicity were not suppressed by fucoidan. Myelosuppression was found to be similar in the fucoidan and control groups. In contrast, general fatigue was detected in 60% of the control group, but was significantly suppressed to 10% in the fucoidan group (Table II).

Patients were followed up at our hospital. The median follow-up period of the 20 patients was 15 months (range 5-27). During the follow-up period, 6 patients (2 in the fucoidan group and 4 in the control group) succumbed due to colorectal cancer progression. The survival of the 10 patients receiving fucoidan treatment was longer than that of the 10 patients in the control group, but the difference was not significant ($P=0.314$, Fig. 1).

Discussion

Fucoidan is one of the major sulfated polysaccharides of brown seaweeds, and it has a wide range of biological activities. Choi *et al* (13) found that fucoidan protects gastric mucosa from inflammatory cytokine-mediated oxidative damage in rats. Hayashi *et al* (7) reported that fucoidan reduces CCl_4-induced acute and chronic liver failure with hepatic fibrosis. The anti-inflammatory activity of fucoidan was demonstrated in rats (14), and fucoidan conferred no toxicity in rats at high doses (15). Thus, fucoidan is anticipated to improve human health, and has been widely distributed as a foodstuff but not as a drug. However, the detailed mechanism of action of fucoidan remains to be verified, and its effects in humans have yet to be determined.

In the present study, we analyzed whether fucoidan protects patients from the toxicity of anti-cancer drugs. Nausea, vomiting, diarrhea, general fatigue and bone marrow suppression are well-known common adverse effects of anti-cancer drugs. Peripheral neuropathy is specific for oxaliplatin. We found that fucoidan suppressed the occurrence of general fatigue in colorectal cancer patients during chemotherapy. It has been demonstrated that fatigue reduces the individual resources of patients, affects their nutritional status, increases morbidity and can have a negative impact on the dose intensity of cancer therapy (16). Iop *et al* (16) reported that fatigue, which was graded using NCI CTC, was detected in almost 30% of patients receiving chemotherapy. In the present study, grade 2 and 3 fatigue was detected in 60% of colorectal cancer patients during chemotherapy. The use of antidepressants may also play a role in the treatment of fatigue, and a number of patients are administered chemical supplements of unproven efficacy. However, no published data exist to confirm this hypothesis. In our study, patients who received fucoidan were able to endure prolonged chemotherapy without fatigue. However, fucoidan did not have an impact on other adverse effects of anti-cancer drugs. The mechanisms that explain chemotherapy-induced fatigue remain to be determined, and no general treatment is currently available to alleviate the symptoms.

Fucoidan has also been found to play a significant role in tumor suppression (17-20). Yamasaki-Miyamoto *et al* (8) and Hyun *et al* (21) showed that fucoidan activates caspase-8 or extracellular signal-regulated kinase and induces apoptosis in tumor cells. These pro-apoptotic effects of fucoidan have not been detected in normal cells. However, no indisputable evidence exists that fucoidan prolongs the survival of cancer patients, even in animal models with human tumor implants. In the present study, although the number of patients was limited and the results were not statistically significant, the prognosis of patients with unresectable advanced or recurrent colorectal cancer was more favorable upon treatment with fucoidan than without. This may be explained by the fact that fucoidan prolonged the duration of the chemotherapy by suppressing the toxicity of the anti-cancer drugs or through an anti-cancer effect of fucoidan itself. Therefore, large controlled studies are required to evaluate the therapeutic effect of fucoidan for unresectable advanced or recurrent colorectal cancer.

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イマチニブの少量長期投与により著明なPRが得られている直腸，胃GISTの2例

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Usefulness of Low-Dose and Long-Term Administration of Imatinib in Patients with Liver Metastases of Rectal GIST and GIST of Stomach: Osamu Kimura, Osamu Yamamoto, Kazunori Hisamitsu, Nariyuki Yamane and Ryuichi Hamazoe
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Summary

Imatinib is an effective drug for KIT positive GIST, and the usual dose is 400 mg/day. On the other hand, imatinib sometimes causes leucopeny and it is hard to maintain a dosage of 400 mg/day. We reported here the two cases with a remarkable response of unresectable GIST using a low-dose and long-term administration of imatinib. It seems that a low dose and long-term administration of imatinib will be an important therapy for unresectable GIST. **Key words:** GIST, Imatinib, PR

要旨 イマチニブ（グリベック）はKIT陽性GISTの治療に有効な分子標的治療薬であるが，通常400 mg/日の投与が一般的となっている。しかし，白血球減少などの副作用も強く，長期間の投与は難しい場合もある。今回，直腸ならびに胃の壁外性巨大GISTに対し，イマチニブ200 mg/日の少量長期投与を継続し，著明なPRが得られた2症例を経験したので報告した。近年，少量長期投与の有効例の報告が散見されるとともに，耐性・PD症例に対する継続投与の意義も報告されており，GISTに対する分子標的治療薬の少量長期継続投与の意義を強調した。

はじめに

gastrointestinal stromal tumor（GIST）はカハールの介在細胞由来の腫瘍であり，多くはc-kit遺伝子の変異による異常なKIT蛋白により増生することが解明されている[1]。また，イマチニブ（グリベック）はこの異常なKIT蛋白の作用を阻害する分子標的治療薬として開発され，奏効率は極めて高率である。しかし，白血球減少などの副作用，経済的理由から十分な投与量，長期間の投与が難しい場合もある。今回，われわれは通常の半量のイマチニブ投与を長期間行い，著明なPRが得られた2例を経験したので文献的考察を加え報告する。

I. 症 例

症例1: 患者は55歳，女性。

主訴: 肛門部痛。

家族歴，既往歴: 特記することなし。

現病歴: 2005年6月ごろより肛門部痛，肛門出血を認め，2005年8月近医を受診，直腸癌を疑われ当院紹介，入院となった。

入院時現症: 身長153 cm，体重49 kg。直腸指診で歯状線直上より始まる弾性硬の全周性巨大腫瘤が認められ，可動性はなく，膣後壁約半周への直接浸潤が疑われた。

治療経過: 血液所見，腫瘍マーカーに異常は認められず，CT検査にて膣浸潤を疑う骨盤内の巨大腫瘤と多発性肝転移が認められた。術前の内視鏡生検では，確定診断が困難であった。このため，2005年9月15日直腸肉腫の膣浸潤と判断し，直腸切断術，子宮付属器・膣後壁合併切除術を施行した。術後の病理組織診断にて，c-kit陽性のGISTと判明した。2005年10月1日よりイマチニブ400 mg/日を開始したところ，白血球減少が認められ9日間の投与で休薬となった。その後，イレウスを来し再手術となったが，11月14日より200 mg/日でイマチニブの投与を再開した（図1）。肝転移巣はイマチニブ

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